REMARKS

Applicants request that the October 20, 2003 Reply to Office Action Under 37 C.F.R. §1.116 (hereafter "the October 20 response") be entered in the instant application.

Applicants thank the Examiner for extending the courtesy of a telephone interview with the undersigned In the interview, the Examiner indicated that it would be helpful if applicants could provide evidence showing that it was known in the art that different pharmacokinetic parameters, such as a patient's total exposure to a drug (area under the time-concentration curve or AUC) or the peak plasma level of the drug (maximum serum concentration or C_{max}), are important for safely and efficaciously treating disease. As discussed below, applicants have done just that.

Pharmacokinetic Properties Associated with Efficacy

It was known in the art at the time the invention was made that various pharmacokinetic parameters were correlated to the efficacy of different drugs in the treatment of disease. For example, a number of studies using different cancer chemotherapeutic drugs have shown that a patient's total exposure to a drug (AUC) or steady-state concentration of a drug is important for efficacy. Calvert et al., J. Clin. Oncol. 7: 1748-56, 1989 (hereafter "Calvert") states that AUC is correlated with therapeutic efficacy for carboplatin, which is used to treat a variety of cancers (see page 1749, left column). In addition, Eksborg et al., Anti-Cancer Drugs 8: 42-47, 1997 (hereafter "Eksborg") states that the cytostatic efficacy of the anthracyclines is correlated with AUC (see page 42, right column). Further, Rodman et al., J. Clin. Oncol. 5: 1007-1017, 1987

(hereafter "Rodman") demonstrates that a high steady-state concentration (C_{ss}) of a cancer chemotherapeutic drug, VM-26, was correlated with increased efficacy (see page 1010, right column and page 1013, left column).

In contrast, studies of different drugs have demonstrated that other pharmacokinetic properties, such as peak plasma level (C_{max}), are primarily correlated with efficacy. For example, Takitani et al., J. Nutr. Sci. Vitaminol. 41: 493098, 1995 suggests that the efficacy of all-*trans*-retinoic acid (ATRA) is correlated with peak plasma levels in pediatric patients with acute promyelocytic leukemia (see pages 496-97). In addition, Gandhi et al., J. Clin. Oncol. 16:3607-15, 1998 (hereafter "Gandhi") shows that the efficacy of arabinosylguanine (ara-GTP) is correlated with peak plasma levels for T-cell acute lymphoblastic leukemia (T-ALL) (see page 3612, right column)

Other pharmacokinetic parameters can also be important for efficacy for some drugs. Shalinsky et al., Investigational New Drugs 16: 303-13, 1999 (hereafter "Shalinsky") demonstrates that antitumor efficacy for a novel MMP inhibitor was dependent upon minimum effective plasma concentrations rather than AUC or C_{max} (see page 310). Eisenhauer et al., Drugs 55:5-30, 1998 (hereafter "Eisenhauer") teaches that the length of time above a threshold paclitaxel concentration was correlated with increased efficacy in lung cancer patients (see page 10, right column).

Studies have also suggested that different pharmacokinetic properties of a drug may be related to efficacy for different diseases. Bruno et al., J. Clin. Oncol. 16: 187-96, 1998 (hereafter "Bruno") states that while a high docetaxel AUC was found to reduce the risk of progression in lung cancer patients, no

significant relationship was found between any estimate of docetaxel exposure and efficacy for breast cancer patients (see page 193, left column). Further, while Gandhi shows that peak plasma levels of ara-GTP were correlated with efficacy for T-ALL, Gandhi also states that the efficacy of ara-GTP was not related with peak plasma levels for a patient with B-cell chronic lymphocytic leukemia (B-CLL) (see page 3612, right column).

Pharmacokinetic Properties Associated with Toxicity

Various pharmacokinetic properties have also been shown to be associated with drug toxicity and, consequently, drug safety. Pharmacokinetic properties identified as being correlated with toxicity include, *inter alia*, AUC, C_{max} and the steady-state concentration of a drug. In many cases, drug toxicity is related to the AUC of the drug. For example, Eisenhauer states that AUC or a certain threshold level of paclitaxel is correlated with toxicity. See page 10, left column. Calvert and Forastiere et al., Cancer Research 48, 3869-3874, 1988 (hereafter "Forastiere") also state that some drugs' toxicities are correlated to their AUC (see page 1749, left column of Calvert, page 3872 and right column of Forastiere). In comparison, Rodman demonstrates that a higher steady-state concentration of VM-26 was correlated to toxicity (see page 1011, left column and page 1013, left column), while Shalinsky states that toxicity for MMP inhibitors is associated with both AUC and C_{max} (see page 312, left column). Further, Eksborg states that C_{max} is associated with toxicity for anthracyclines, a class of cancer chemotherapeutics (see page 42, right column).

These studies demonstrate that various pharmacokinetic parameters of a number of cancer chemotherapeutic drugs are associated with efficacy and safety of those drugs. Further, Gandhi and Bruno also appear to suggest that different pharmocokinetic properties of the same drug may be important for efficacy of distinct diseases. Therefore, these studies provide evidence that it was known in the art that various pharmacokinetic parameters are important for safely and efficaciously treating disease.

Conclusion

Applicants request that the Examiner consider the foregoing remarks together with the October 20 response, allow the pending claims and pass this application to issue.

Respectfully submitted,

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